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Fragment Library Design, Synthesis & Expansion: Nurturing a Synthesis and Training
Platform

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Key Words: fragment-based drug discovery; compound library; physicochemical
properties; scaffold; drug discovery.

Teaser: We describe an approach to develop diverse and novel fragment libraries,
which can also be used as a training platform for medicinal chemists, at the
undergraduate and graduate levels.

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ABSTRACT: The availability of suitable diverse fragment- and lead-oriented screening compounds is key for the identification of suitable chemical start points for drug discovery programs. The physicochemical properties of molecules are critical in determining the success of small molecules in clinical development, yet reports suggest that pharmaceutical and academic sectors often produce molecules with poor drug-like properties. We present a platform to design novel, high quality and diverse fragment and lead-oriented libraries with appropriate physicochemical properties in a cost-efficient manner. This approach has the potential to assist the way libraries are constructed by significantly addressing the historical uneven exploration of chemical space for drug discovery. Additionally, this platform can teach both undergraduates and graduates compound library design.

INTRODUCTION

Fragment-based drug discovery (FBDD) and high throughput screening are important approaches to find chemical start points for drug discovery programmes. These libraries rely on synthesis as well as commercial acquisition of new compounds. The majority of this extensive effort, mainly carried out over the last 10-15 years, remains unpublished, as novel proprietary compounds provide a competitive edge for the respective pharmaceutical companies. Hence, there is no full understanding of the proportion of chemical space [1,2] covered by current compound libraries and screened in biological assays. It is estimated that there are more than 10^{60} possible organic compounds that fulfill Lipinski's rules [1,3]. However, a framework analysis of the CAS Registry suggests that chemists are more likely to use a particular framework to make a compound, the more often that framework has been used in the past [4]. This results in the proliferation of certain frameworks and limits the exploration of novel chemical space.

Bemis and Murcko analyzed drug molecules according to ring, linker, framework and side chain atoms so that the information could be employed for the synthesis of new scaffolds with biological rationale [5,6]. Their analysis suggests that the scaffold and side chain diversity associated with known drugs is relatively low. More recently, analysis of drug space (until end of 2012) by Taylor et al., describing the rings and

1
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3 molecular scaffolds [7], showed that there were only 351 ring systems and 1197
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5 frameworks. Further, only six new ring systems enter drug space each year and 28% of
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7 new drugs contain a new ring system. This is a relatively small number compared, for
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9 example, to the predicted number of small aromatic rings [8]. Increasing the diversity
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11 and novelty of compound libraries is likely to be important in probing the drug-like
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13 chemical space that addresses biological space [2], to tackle both existing and emerging
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15 drug targets (for example protein-protein interactions).
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24 For many drug discovery organizations, particularly small- and medium-sized
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26 enterprises (SMEs) and the public sector, access to chemical matter is largely reliant on
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28 commercially available fragment and lead-like libraries. However, a recent analysis has
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30 suggested that “existing synthetic methodology is unintentionally predisposed to
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32 producing molecules with poorer drug-like properties and that this is likely to have
33
34 ramifications to the early hit- and lead-finding phases of the drug discovery process”
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36 [9], particularly in addressing emerging target classes. In contrast, academic synthetic
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38 chemists are developing new synthetic methodology, which would be a powerful way
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40 to increase the novelty and diversity of our chemical libraries, if leveraged for
41
42 compound library synthesis. This could be particularly beneficial for SMEs and academic
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44 drug discovery groups, as well as the pharmaceutical industry (Figure 1) [10].
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3 Fragment-based drug discovery (FBDD) is an important approach to identify new
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5 leads for drug discovery [11-14]. It has the advantage of being able to address an area
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7 of chemical space with many fewer compounds than conventional lead-like or drug-like
8
9 libraries. During an attempt to increase the chemical diversity of our fragment library,
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11 we realized that relatively simple derivatization (“capping”) of commercially available
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13 building blocks could expand into new areas of chemical space that are not
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15 commercially available, often with very different chemical and physicochemical
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17 properties (Figure 2), [15]. These compounds could subsequently be rapidly expanded
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19 into lead-like space for hits, using the same or similar chemistry. We therefore decided
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21 to establish a platform to design and generate compounds to address a wider range of
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23 fragment-space. This platform encompasses a set of criteria for compound design, and
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25 procedures for compound preparation and carrying out quality assurance.
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40 FBDD typically uses structural knowledge for fragment optimization using a range
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42 of strategies including merging, linking or growing [12]. Fragments typically bind to “hot
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44 spots” within the ligand binding site of the target [16] and options for optimization are
45
46 prioritized according to synthetic appeal, opportunity to access relevant areas of the
47
48 binding site, binding affinity and ligand efficiency. The prioritized fragments are then
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50 typically elaborated through addition of a suitable functional group, or “chemical
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52 handle”, to attach and elaborate the new substituent to identify further interactions
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[11]. Ideally the chemical handle provides additional interactions within the target to improve affinity as well aid both fragment growth and linking.

Screening fragments with “built-in” handles has the potential for additional interactions with the target (protein) and faster elaboration of a fragment. However care has to be taken as increasing complexity in a fragment decreases the probability of it achieving optimal ligand - protein interactions [17]. Conversely, too little complexity can lead to interesting interactions being missed [18]. Therefore, a careful balance is required between the “built-in” handles and the complexity of the fragment. Subsequent introduction of a chemical handle to a fragment may alter the binding conformation. This was demonstrated by Shoichet et al., who showed that deconstruction of a larger potent β -lactamase inhibitor into small fragments with “minimal complexity” does not necessarily recapitulate its binding to the enzyme [19]. However, fragments with additional functional-group complexity could recapitulate the larger potent β -lactamases inhibitor binding. Conversely, smaller fragments could identify more ligand efficient binding modes to the “hot spot”, which after alternative optimization strategies, could potentially lead to development of compounds with better drug-like properties e.g. lower molecular weight.

A case study in support of the use of fragments with pendent functional groups suitable for rapid elaboration comes from Nazaré et al. [20] who demonstrated the

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3 super-additivity effect of linking two fragments (derived from deconstructing a potent
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6 factor Xa inhibitor) containing amide and sulfonamide functional groups respectively
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9 (Figure 3).

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12 To make maximum use of the fragment library, an ideal scenario would be to have
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15 a linkage between the scaffolds in a fragment library and a lead-like library. This would
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18 have two advantages: firstly, a hit in a fragment screen could be rapidly expanded into
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21 lead-like space using analogues of the scaffold in the lead-like library, or using known
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24 robust chemistry to grow the fragments. Secondly, if there is a hit on screening a lead-
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27 like library, this could be rapidly “de-constructed” into fragments to probe the key
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30 receptor-ligand interactions. Given the rapid increase in the number of possible
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33 compounds as the heavy atom count in a molecule increases, there will be a limit to the
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36 examples of a fragment-scaffold that can be in a lead-like library. Therefore, it will be
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39 important to have chemistry suitable for fragment-scaffold elaboration.
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45 46 RESULTS AND DISCUSSION

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49 **Design Process.** A key component of our library platform was to identify under-
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52 represented areas of commercial chemical space and create diversity based on
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55 functional group manipulation. A library design team, composed of experienced
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58 medicinal chemists, investigated a number of procedures for synthesis of fragments
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3 with differing synthetic complexity, based on the analysis of fragment scaffolds in
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6 relation to published biologically relevant data. Our workflow is shown in Figure 4.
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10 We had three start points to develop novel fragments (Figure 5): (1) in-house
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12 assembly of diverse monomer (appendage) sets, which could be functionalized into
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14 both fragment and lead-like libraries, (2) commercial and in-house project
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16 intermediates, and (3) novel chemical scaffolds. Designs were filtered to ensure that
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18 compounds selected for synthesis filled in “gaps” in chemical space in our current
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20 fragment library.
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28 Our focus here was on producing fragment and lead-like libraries to identify non-
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30 covalent, reversible inhibitors. Functional groups known to be chemically reactive or
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32 toxic were removed (so called “Structural Alerts”), as were compounds reported to be
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34 pan assay interference compounds (PAINS) [21]. Supporting information includes the
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36 Drug Discovery Unit revised in-house [22] and modified Eli Lilly-published [23]
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38 structural alerts and the PAINS alerts. After applying the structural alerts, we then set
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40 about defining descriptors and selection criteria for non-covalent reversible fragment
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42 libraries, monomer sets and lead-like libraries (Table 1). We report the final version we
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44 now use, which is the result of several rounds of iteration and optimization of the
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46 library selection parameters; so several of the early libraries were designed with slightly
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48 different criteria.
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3 Although a number of key reports have evaluated the impact of aromatic ring
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5 count [24-26] and Fsp³ on solubility and compound developability within drug-like
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7 chemical space [27,28], in practice, we did not explicitly factor in the aromatic ring
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9 count, as the other parameters took care of this. As historical fragment libraries
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11 (including our own) sample limited shape diversity [15], which in practice may impact
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13 opportunities to introduce shape diversity [29], we introduced routine calculations of
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15 the principal moments of inertia (PMI). Computational tools of evaluating novelty and
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17 diversity included ECFP4 fingerprint analysis, principal component analysis (PCA) and
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19 commercial availability versus established libraries (see Table 1).
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30 **Monomer Set Selection.** Diverse monomer appendage sets were compiled to
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32 support our early hit- and lead-finding phases. The process for diverse monomer
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34 appendage set selection and purchase has evolved with the selection of each monomer
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36 set and was often dovetailed to the availability from the internal inventory. For
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38 example, selection of approximately 60 diverse primary and secondary amines included
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40 the following:
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- 49 1. Extracting amines from the eMolecules database, salt stripping and filtering based
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51 on commercial availability from a set of suppliers (Aldrich, Enamine, Fluorochem,
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53 Tyger, Acros, Chembridge, Key Organics, ChemDiv, Otava and Maybridge, Combi-
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55 Blocks and Frontier)
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2. Filtering compounds based on the properties described in Table 1 for monomer sets, which included in-house curated structural alerts.
3. Clustering of the filtered compounds using the ECFP4 fingerprint and binning by molecular weight for visual selection by a focused group of experienced medicinal chemists.
4. Purposely skewing the selection towards the lower molecular weight range within each cluster, to provide a greater diversity of cores of varying molecular weight and physicochemical properties.
5. A final set selection by further splitting into bins to ensure maximal coverage of both fragment and lead-like chemical space: 30 monomers were selected with $MW \leq 120$, 20 with $120 < MW < 160$ and 10 with $160 < MW \leq 200$.

We selected subsequent monomer sets in a similar manner and have thus far included carboxylic acids, sulfonyl chlorides and aldehydes. Learning from initial experience resulted in the monomers being enumerated after the initial filtering of the eMolecules search to afford the capped products and then examples taken from each cluster by chemist's eye selection. Cost, commercial availability and specific project requirements were factored into the final design of monomer sets.

Monomer Set Capping Fragment Library Design. Since the monomer sets were diverse, as defined by fingerprint analysis and visual inspection, we considered that “minimal functional group transformation” would give a diverse selection of functional group containing fragments (see Figure 6). Based on the case study by Nazaré et al., [20] the initial project focused on acetylation and mesylation of the amine monomer set and relevant inventory amines (see Scheme 1).

We employed the following protocol to identify the most suitable fragments for synthesis and selected examples of the acetylated and mesylated amine monomer set are shown in Charts 1 and 2:

1. Enumeration to give the acetylated and mesylated products.
2. The virtual products were filtered according to the fragment properties in Table 1.
3. Structural alert filters (PAINS, Eli Lilly and in-house) were applied [21-23].
4. Filtered compounds were clustered using the ECFP4 fingerprint (0.5 Tanimoto).
5. Commercial availability of the exact compound within the eMolecules database was checked. In general, we avoided re-making commercially available compounds. However sometimes when the compound was part of an array, it was cost-effective to include it.

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3 6. Tanimoto similarity of each compound to the current fragment library was
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6 calculated; however this was treated as a guide and all structures were inspected
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9 by a medicinal chemist before preparation.
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12 7. PCA (ECFP4) and PMI plots were generated for enumerated products to better
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15 understand the chemical diversity.
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22 In our platform, designed compounds were synthesized through in-house
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24 chemistry or through outsourcing. The fragment functional group capping initiative, as
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26 part of an academic-based drug discovery unit, provided an excellent opportunity to
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28 nurture undergraduate students on how to design and synthesize fragments.
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30 Undergraduate project students were paired with a mentor and provided with a set of
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32 enumerated fragments for a particular monomer set coupling reaction. Guiding of
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34 students by the mentor through the selection process, provided valuable training in the
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36 use of modern *in silico* prediction (StarDrop™ (www.optibrium.com)) and visualization
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38 (Vortex) software. The reagent sets were then selected and the students guided to
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40 identify robust and safe synthetic routes for parallel synthesis. The optimal synthetic
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42 route was identified with a trial set of compounds and the library was then prepared
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44 using parallel techniques, starting with 6 compounds and progressing towards 24
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46 compound arrays. As well as using the monomer sets, this approach was extended to
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commercially available building blocks and appropriate in-house project intermediates.

This platform also has the advantage from a training context of being tunable, ranging from straightforward functional group interconversion to more complex scaffold synthesis.

We extended the approach to a number of other types of chemistry, including urea formation (Figure 6) and cross-coupling of the monomer sets. This was rolled out initially to final (fourth) year project students, working in our laboratories and then subsequently to third year undergraduate students. The students gained a significant training in the parallel synthesis and purification of small polar compounds and excitement stimulated by production of novel compounds.

Synthesis of Multiple Diverse Scaffolds from Common Intermediates. The next step was to identify flexible platforms for the synthesis of multiple unexplored diverse fragment scaffolds from readily available key intermediates. A pilot platform was based around the evaluation of fused bicyclic fragment frameworks described by Bemis and Murcko [5,6], in particular 6,5- and 6,6-fused bicyclic scaffolds, with the requirements of a saturated ring and sp^3 vectors with diverse functional groups capable of forming varied pharmacophoric points. To better understand the existing landscape for such scaffolds, we conducted database searches and refined the output based on

commercial availability as well as property selection filters based on our guide criteria for fragment selection within Table 1. A selection of the output in Figure 7 shows an uneven distribution of the explored potential chemical space for a selected set of different vectors as well as decreased representation because of increased structural complexity through the addition of chirality and heteroatoms into the saturated six-membered ring. From the authors' experience, the fact that a compound is offered commercially does not necessarily mean it is readily available at a suitable cost, as compound suppliers often assign a synthesis time based on literature routes and a minimum scale. In our opinion, the output in Figure 7 provides a balanced approach for identifying compounds that may be available and are likely to be accessed via literature synthetic routes.

To sample wide chemical space, we opted to identify common intermediates that could be prepared on a large scale and readily expanded into multiple structurally complex and diverse unexplored scaffolds. This approach led us to evaluate cyclic ketone building blocks, based on validated literature chemistry to make tetrahydroquinazoline, tetrahydroindazole and tetrahydrobenzothiazole 6,5- and 6,6-fused bicyclic scaffold derivatives. These derivatives were targeted from three simple commercially available ketone starting materials, ethyl 4-oxocyclohexanecarboxylate (**21**: X = CH₂CO₂Et), *N*-Boc-4-piperidone (**22**: X = NBoc), and *N*-4-Boc-

aminocyclohexanone (**23**: X = CHNHBoc), which were subsequently converted into diverse fused ring systems using divergent synthetic protocols (Scheme 2). These included α -substitution with *N,N*-dimethylformamide dimethyl acetal (DMF–DMA) to provide the corresponding enones **24–26** (**24**: X = CHCO₂Et, **25**: X = NBoc, and **26**: X = CHNHBoc) and α -monobromination with Br₂ to afford α -bromo ketones **27–29** (**27**: X = CHCO₂Et, **28**: X = NBoc, and **29**: X = CHNHBoc).

Acid-catalyzed cyclization of enone **24** with *S*-methylisothiourea afforded the 2-(methylthio)-tetrahydroquinazoline **30**, which was subsequently oxidized with *m*-chloroperoxybenzoic acid (*m*-CPBA) to the corresponding sulfone **31**. The reactive 2-(methylsulfonyl) group of **31** was treated with ammonia, dimethylamine, and methylamine to access amines **32** (R₁ = R₂ = H), **33** (R₁ = R₂ = Me), and **34** (R₁ = Me, R₂ = H) respectively.

Cyclization of enones **25** and **26** with the appropriate guanidine salts (Scheme 2), guanidine carbonate, 1,1-dimethylguanidine sulfate, methylguanidine hydrochloride provided a corresponding set of minimal amino-derived fragments **35** (X = NBoc, R₁ = R₂ = H), **36** (X = CHNBoc, R₁ = R₂ = H), **37** (X = NBoc, R₁ = R₂ = Me), **38** (X = CHNBoc, R₁ = R₂ = Me), **39** (X = NBoc, R₁ = Me, R₂ = H), and **40** (X = CHNBoc, R₁ = Me, R₂ = H). Treatment of enones **24–26** with hydrazine hydrate afforded indazoles **41–43** (**41**: X = CHCO₂Et, **42**: X = NBoc, and **43**: X = CHNHBoc), whereas coupling of α -bromo ketones **27–29** with

thioacetamide led to thiazoles **44–46** (**44**: X = CHCO₂Et, **45**: X = NBoc, and **46**: X = CHNHBoc) (Scheme 2). Further reactions from these common intermediates could also be envisaged, such as reaction of enones **24–26** with hydroxylamine, cycloaddition reactions of the enones **24–26**, or Robinson annulation of **21–23**, followed by subsequent chemistry or building diverse ring systems from the ketone intermediates **21–29** (Scheme 2).

However for this study, having created a platform of diverse scaffolds, we next turned our attention on how to best represent potential larger lead-like arrays, by increasing functional group diversity and applying “capping” chemistry to generate more diverse fragments or to move them into lead-like space. To further diversify the functional groups of the 15 scaffolds in a parallel fashion, esters **32–34**, **41**, and **44** were reduced using lithium aluminium hydride to afford the corresponding alcohols **47–51** or hydrolyzed with NaOH to give acids **52–56**. Acids **53**, **54**, and **56** were further coupled with methylamine or dimethylamine to afford the primary methyl amides **57–59**, or the corresponding secondary dimethyl amides **60–62** respectively (see Scheme 3).

Further examples are included in the Supporting Information. Of course many other derivatizations can be applied to the scaffolds in Scheme 3, such as reductive amination, ether formation, conversion of the carboxylate to a five-membered heterocycle, and so forth.

The above functional group modifications provided a more even sampling of potential pharmacophores for these 6,5- and 6,6-fused bicyclic scaffolds. These initial scaffolds are limited to a specific vector; however, we envisage that the methodology can be extended to different vectors, saturated ring sizes as well as further addition of heteroatoms into the saturated ring system.

Evaluation of the Compounds. PCA (ECFP4) analysis of these diverse fragments showed that they were significantly different from the historical fragment library (Figure 8a). This was considered largely to be as a result of the synthetic design to incorporate a heteroaromatic ring fused to a sp^3 -saturated ring with a chiral vector of varied functional groups. PMI analysis was used to evaluate the 3D diversity of the fragments, due their relatively limited numbers of conformations due to their small size (Figure 8b) [30]. These fragments do not probe the more sphere-like region of the PMI plot, as the vectors explored provided a degree of rod- and disc-shaped character, but it is key to emphasize that these fragments are not flat and highly conjugated due to their design strategy (Figure 8c). To ensure that the new fragments were distinct from our historical fragment library, an ECFP4 fingerprint with a Tanimoto cutoff ≤ 0.6 was generally employed, although some compounds with higher Tanimoto similarity were included following visual analysis. Commercial availability (i.e., novelty) was determined

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3 by searching eMolecules (Figure 8f); revealing that many compounds were not
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5 commercially available, enabling exploration of novel fragment chemical space.
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9 Evaluation of the commercial availability, shape and diversity for a range of the
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11 fragment sets synthesized to date are shown below, together with highlights of selected
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13 molecules (Figure 9).
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18 **Plating, Quality Control, Solubility, and Stability.** Compound quality and handling
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20 are key to the successful deployment of any screening library. This is particularly true in
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22 the area of fragment-based lead discovery where fragments may be routinely screened
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24 at concentrations up to 1 mM. When screening at such a high concentrations small
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26 amounts of impurity, can have a significant impact on the false positive rate and can
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28 lead to the wasteful deployment of valuable resources. To minimize wasted time and
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30 effort spent on following up artifacts, we established the following practices for quality
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32 control and compound handling.
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43 Upon synthesis, fragments were routinely analyzed from solid by ^1H NMR and LC–
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45 MS to confirm identity and ensure appropriate purity (> 95%) before registration in our
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47 compound management database. At this point the weighed sample was submitted to
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49 our compound-handling group and the data captured in the database used to drive
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51 solubilization protocols for preparation of stock solutions and samples for further
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53 characterization. Further characterization involved the collection and analysis of one-
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dimensional NMR spectra of an approximately 2 mM solution of the compound in phosphate buffer with suppression of the water signal by excitation sculpting [31]. Analysis of this data allowed further confirmation of identity, purity (> 95%) and allowed us to generate an estimate of solubility based on a comparison of the intensity of the compound signal with the DMSO-d₅ peak. Water-LOGSY was also acquired for each compound to assess the levels of self-aggregation [32]. Further physicochemical characterization included kinetic solubility, by assesses the compound solubility in the range of 250 μM to 1 mM, and CHI logD (pH7.4) data on selected fragment. As expected, based on the *in silico* design predictions, the kinetic solubility was overall very good for the majority of the compounds, with only a handful with kinetic solubility between 250 μM to 1 mM (Figure 10a). Since fragment and lead optimization based drug discovery programs commonly use ligand efficiency metrics based on *in silico* predictions of logP and logD, we also obtain a good understanding of the correlation between measured and *in silico* predicted values for a scaffold at an early stage. The coefficient of determination (R^2) for a plot of the *in silico* predicted logD (Stardrop™) versus measured CHI-logD (pH7.4)[33] for fragments with a suitable chromophore, showed a moderate correlation (Figure 10b) [34]. This data is helpful when making choices between fragment hits and facilitates better in-house CHI-logD predictions for hit expansion and lead orientated synthesis.

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3 To ensure that compound quality is maintained throughout the lifetime of the
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5 library, a strict compound-handling regime has been implemented. Fragments are
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7 solubilized and held as a 200 mM DMSO solution in master plates. These master plates
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9 are used to create multiple daughter plates that are sealed and stored in low-humidity,
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11 are used to create multiple daughter plates that are sealed and stored in low-humidity,
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13 inert atmosphere at -20°C until required. Once in use, each daughter set is stored at
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15 room temperature and used for a maximum of six months. This important part of our
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17 compound management workflow minimizes the significant degradation that may be
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19 encountered when subjecting screening sets to multiple freeze–thaw cycles [35]. An
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21 important part of any fragment screening protocol would be confirmation of activity
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23 with fresh material that has been properly checked for identity and purity.
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36 CONCLUSION

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39 A successful academic-based platform has been set up to nurture both
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41 undergraduates and graduates to understand the importance of physicochemical
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43 properties in the design and synthesis of novel polar fragments. This powerful, yet
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45 general design and synthesis platform provides a much needed source of novel high-
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47 quality diverse fragments to complement our internal library enhancement efforts. To
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49 date this platform has delivered 356 diverse compounds within our selected criteria.
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52 Screening of these compounds has already led to the identification of fragment hits and
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the results will be presented at a future date. We intend to apply the lessons learned from current and future screens to feedback into the design and selection process. As such, we continue to expand our platforms to synthesize diverse scaffolds from common bulk intermediates, develop diverse monomer sets to support internal drug discovery programs as well as generate novel fragment and lead-like arrays through the training of undergraduates and graduates. Expansion of such platforms within the academic sector could significantly address the historical uneven exploration of chemical space and improve access to high quality and diverse fragment and lead-like chemical matter. Such an effort should significantly improve the probability of success for both academic- and industrial-based translational research and we are open to collaborate with parties interested in adopting or supporting such platforms. Whilst preparing this manuscript, we were encouraged to see the recent publication of a conceptually similar approach by Marsden *et. al.* towards the synthesis of diverse scaffolds that can be elaborated into novel lead-like chemical space [36].

Notes

The authors declare a collaboration with Key Organics (<http://www.keyorganics.net/>) to make fragments (which have passed the plating, quality control, solubility and stability

criteria) available for purchase, with the view of investing proceeds into additional design and synthesis platforms.

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ABBREVIATIONS

Ar, aromatic; CHI, chromatographic hydrophobicity index; DIPEA, *N,N*-diisopropylethylamine; ECFP4, extended-connectivity fingerprints; FG, functional group; Fsp³, sp³ fraction; HAC, heavy atom count; RotB, rotatable bonds, Water-LOGSY, water-ligand observed via gradient spectroscopy.

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Figure 1. The importance of synthetic methodology to provide fragment, lead-like and drug-oriented libraries to initiate and drive translational drug discovery.

Figure 2. The effect of “capping” a carboxylic acid can give rise to a number of different pharmacophores.

Figure 3. Nazaré et al.[20] case study showing the superadditive effect of linking amide and sulfonamide functionalized fragments to afford a potent factor Xa inhibitor.

Figure 4. Typical workflow. The precise order of steps was sometimes varied.

Figure 5. Strategy for compiling fragment and lead-like libraries.

Figure 6. Example monomer sets and minimal functional group transformations.

Figure 7. Database substructure searches for selected 6,5- and 6,6-fused bicyclic scaffolds with a functional group, based on commercial availability as well as property selection filter ($MW \leq 250$, $LogP \leq 2.5$, $HBD \leq 3$, $HBA \leq 6$, $PSA \leq 90 \text{ \AA}$, $RotB \leq 3$).

Figure 8. (a) PCA of synthesized diverse scaffolds (green) vs original fragment library (grey). (b) PMI plot of synthesized diverse scaffolds (green) vs original fragment library (grey). (c) Fsp3 of synthesized diverse scaffolds. (d) Intralibrary Tanimoto similarity of synthesized diverse scaffolds using the ECFP4 fingerprint. (e) Fsp³ of original fragment library. (f) Commercial availability of synthesized diverse scaffolds (eMolecules).

Figure 9. (a) PCA of capped monomer sets (green) vs original fragment library (grey). (b) PMI plot of capped monomer sets (green) vs original fragment library (grey). (c) Fsp³ of capped monomer sets. (d) Intralibrary Tanimoto similarity of capped monomer sets using the ECFP4 fingerprint. (e) Fsp³ of original fragment library. (f) Commercial availability of synthesized capped monomer sets (eMolecules).

Figure 10. (a) Kinetic solubility versus *in silico* predicted logD. (b) *in silico* predicted logD versus measured CHI-logD (pH7.4), showing the line of unity.

Scheme 1. Acetylation and mesylation of the amine monomer set and inventory amines: Reagents and conditions: (a) CH₃COCl, DIPEA, DCM, rt; (b) CH₃SO₂Cl, DIPEA, DCM, rt.

Scheme 2. Synthesis of 6,5- and 6,6-fused bicyclic scaffold derivatives. Reagents and conditions: (a) DMF–DMA, Et₃N, microwave irradiation at 130 °C for **24**, or DMF–DMA, toluene, 100 °C for **25** and **26**; (b) Br₂, AlCl₃, MeCN (**27**) or EtOAc (**28** and **29**), 0 °C → rt; (c) *S*-methylisothiourea, 4 M dioxane HCl solution, DMSO, 130 °C; (d) *m*-CPBA, DCM, rt; (e) 33% aqueous NH₃ solution, dioxane, microwave irradiation at 160 °C for **32**, or dimethylamine and methylamine, THF, microwave irradiation at 160 °C for **33** and **34**; (f) guanidine carbonate, KOAc, EtOH, microwave irradiation at 100 °C for **35** and **36**, or 1,1-dimethylguanidine sulfate, and methylguanidine hydrochloride, Cs₂CO₃, DMSO, 80 °C for **37–40**; (g) NH₂NH₂, H₂O, EtOH, 40 °C (**41**), or rt (**42** and **43**); (h) thioacetamide,

DMF, 80 °C for **44**, or thioacetamide, EtOH, microwave irradiation at 100 °C for **45** and **46**.

Scheme 3. Capping chemistry to increase diversity. **Reagents and conditions:** (a) LiAlH_4 , THF, rt; (b) NaOH, MeOH, reflux; (c) methylamine (**57–59**) or dimethylamine (**60–61**), DIPEA, PPA, DCM, rt; (d) TFA, DCM, rt; (e) CH_3COCl (**64** and **67**) or $\text{CH}_3\text{SO}_2\text{Cl}$ (**65** and **68**), DIPEA, DCM, rt.

Chart 1. Selected fragments from acetylation of the amine monomer set

Chart 2. Selected fragments from mesylation of amine monomer set

Table 1. Descriptors and guide selection criteria employed for non-covalent reversible fragment libraries, monomer sets and lead-like libraries

Peter Ray



Peter Ray graduated from University of Cape Town then completed an industrial MSc fellowship working on estradiol analogues. Moved to the UK to complete his PhD at the University of Liverpool before moving to the University of Nottingham for a lecturer position. Joined Amura Therapeutics working on Cathepsin inhibitors, then Organon (which became Schering Plough-MSD) working as a project leader in multiple therapy areas. Moved to UCB as a Group Leader and is currently the Tuberculosis Project lead at the University of Dundee Drug Discovery Unit where he has helped evolve the fragment and library expansion programs.

Ian Gilbert



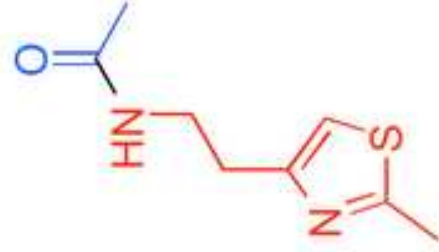
Ian is Head of Medicinal Chemistry in the Drug Discovery Unit, which he helped to set up on moving to Dundee in 2005. Ian started his research career with a PhD in synthetic chemistry, working with Andrew Holmes at the University of Cambridge (1990). This was followed by a post-doctoral fellowship with Parke-Davis Research, before spending a year teaching chemistry at the University of Zambia. On returning to the UK, Ian worked on a chemical biology project at the University of Cambridge, before establishing his own independent medicinal chemistry research group at the Welsh School of Pharmacy in Cardiff University, focusing on drug discovery for neglected tropical diseases.

Paul Wyatt

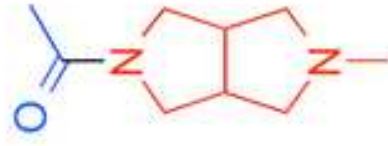


Professor Paul Wyatt's role as Head of Drug Discovery Unit, University of Dundee, UK is to develop translational research at Dundee, by bringing together the DDU's expertise of Drug Discovery in the Pharma/Biotech sector with basic academic research to de-risk novel targets for drug discovery and deliver new treatments for diseases including, TB, malaria, cancer and rheumatoid arthritis.

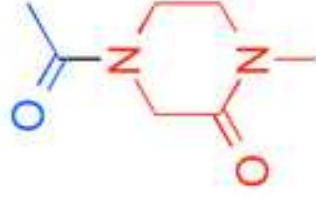
Previously Paul worked in the BioPharma industry for 23 years; playing a significant part in seven compounds entering pre-clinical development. Paul obtained his BSc and PhD in Chemistry from the University of Birmingham. Paul is an author on over 50 papers.



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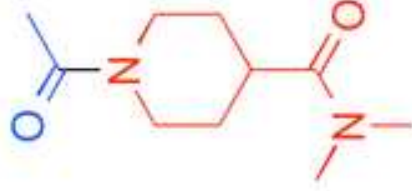
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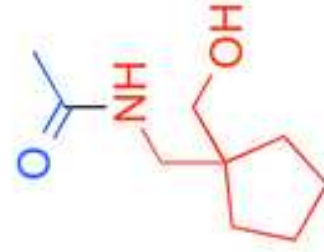
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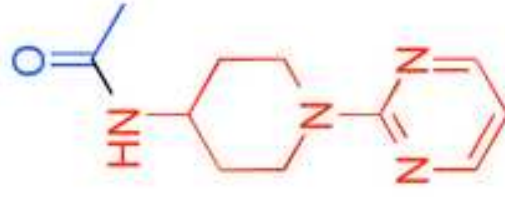
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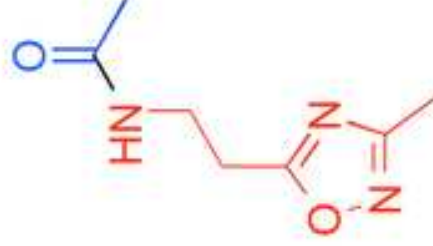
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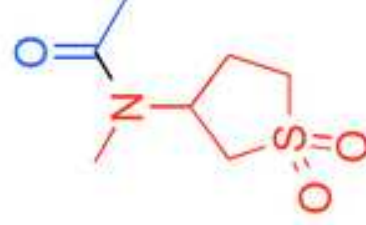
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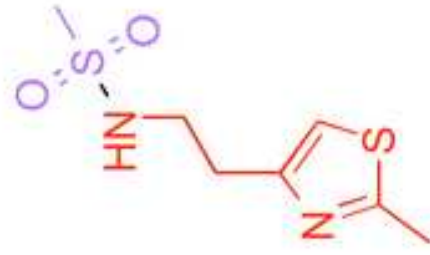
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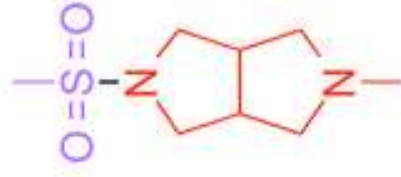
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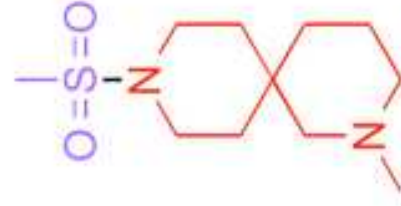
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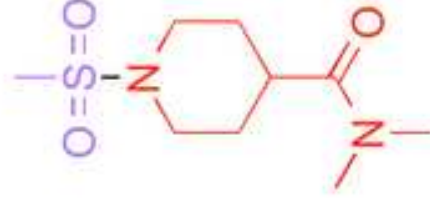
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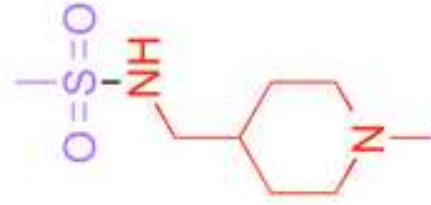
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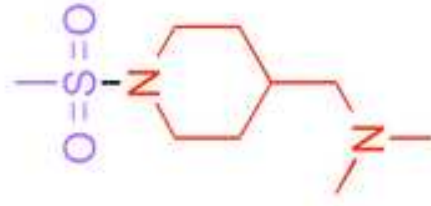
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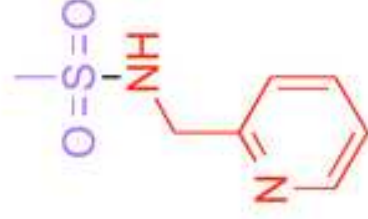
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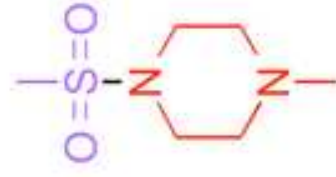
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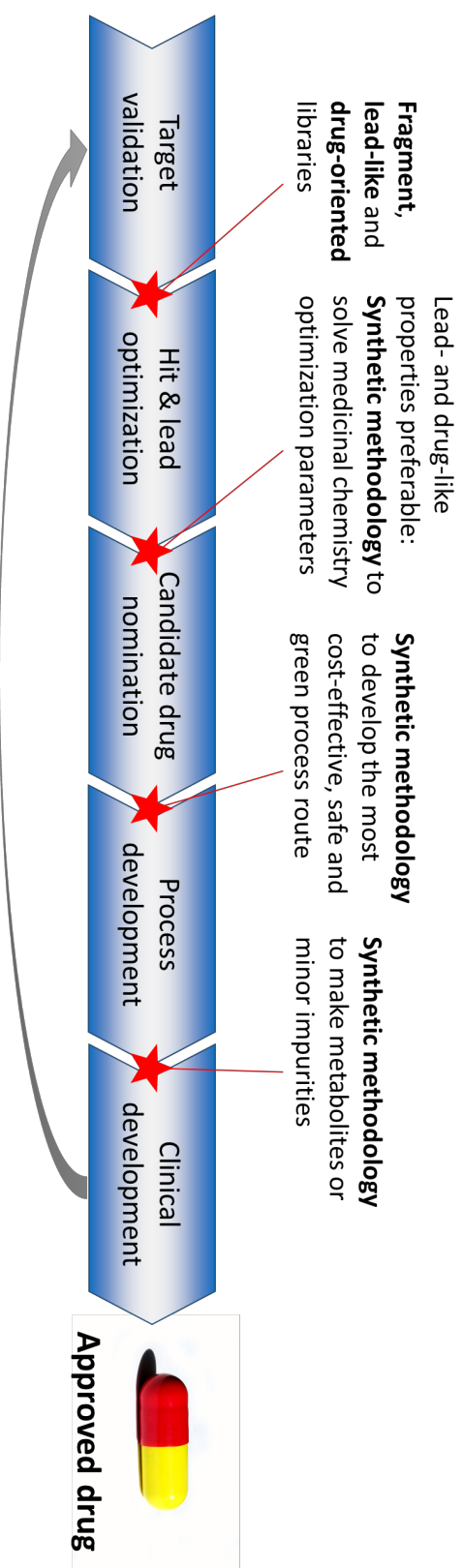


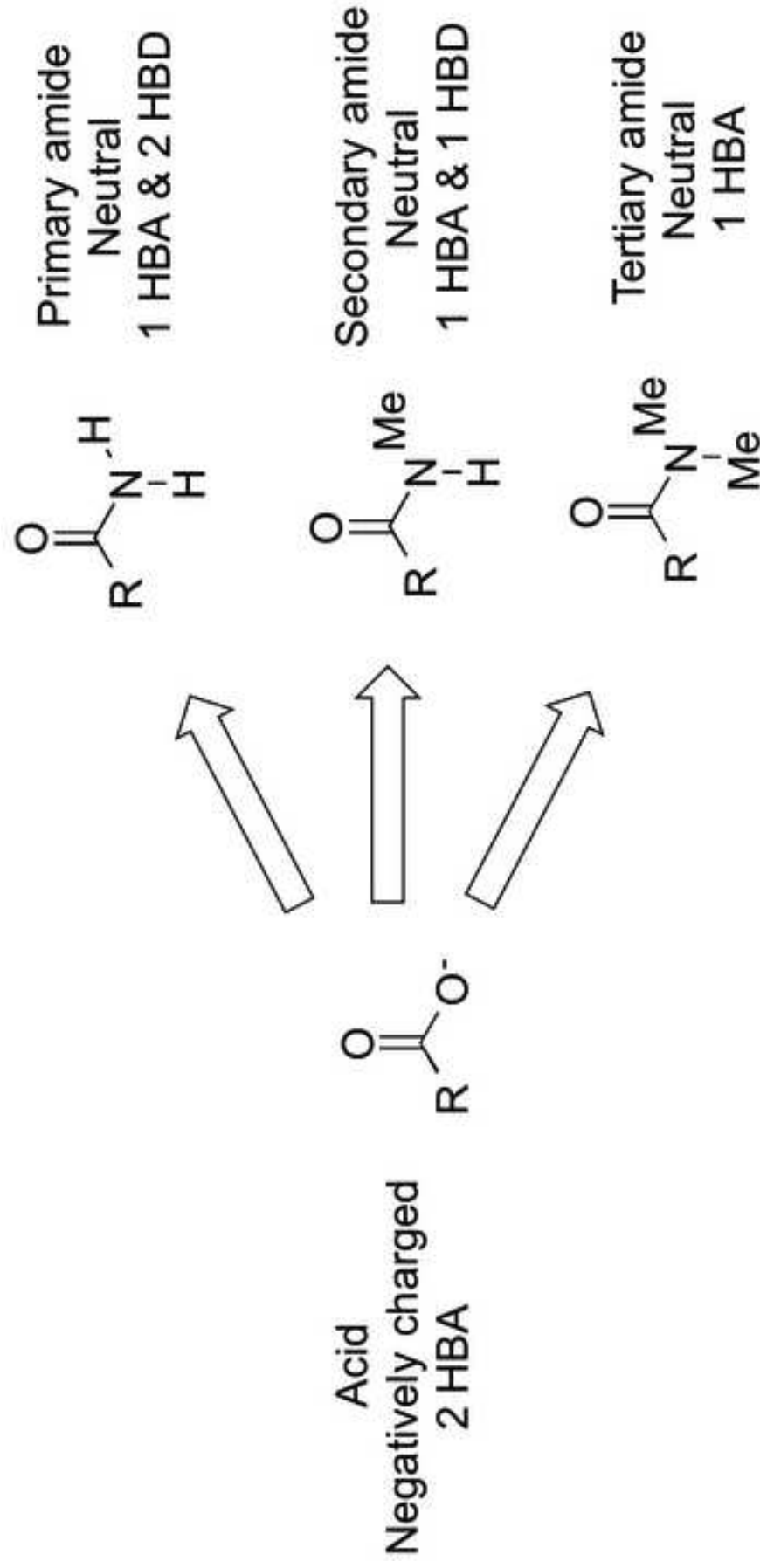
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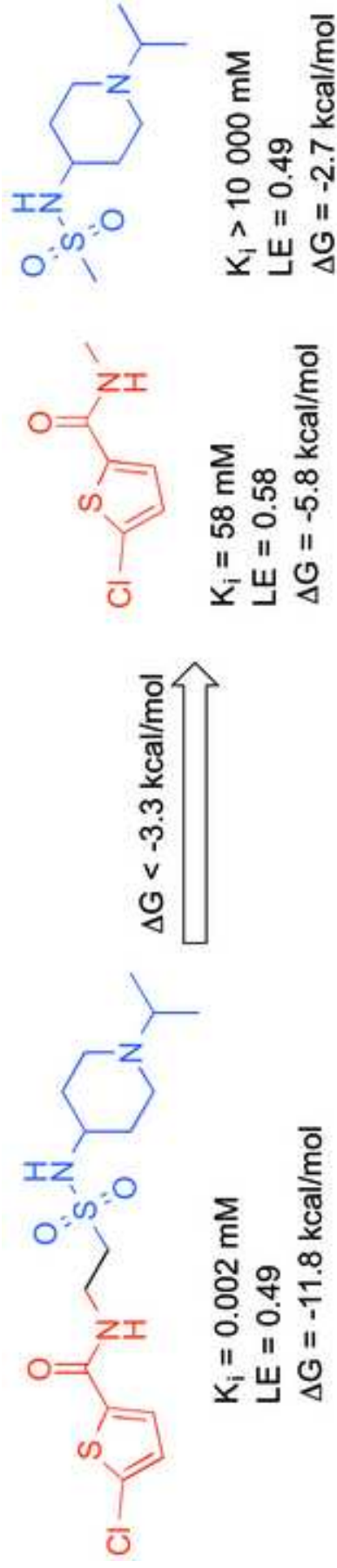
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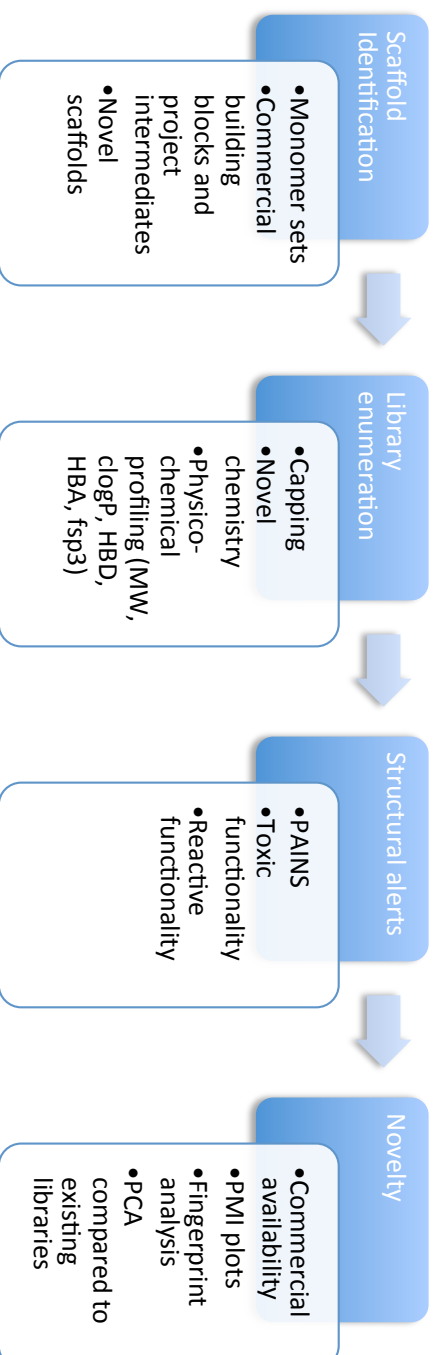


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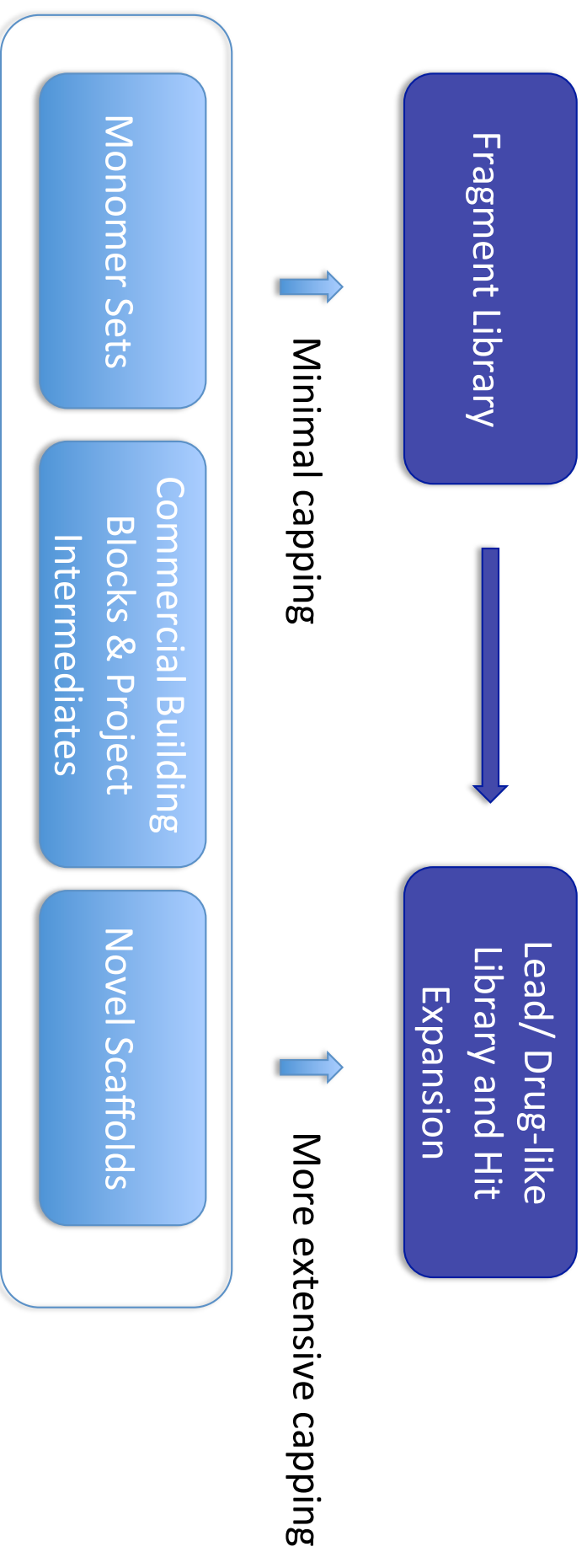
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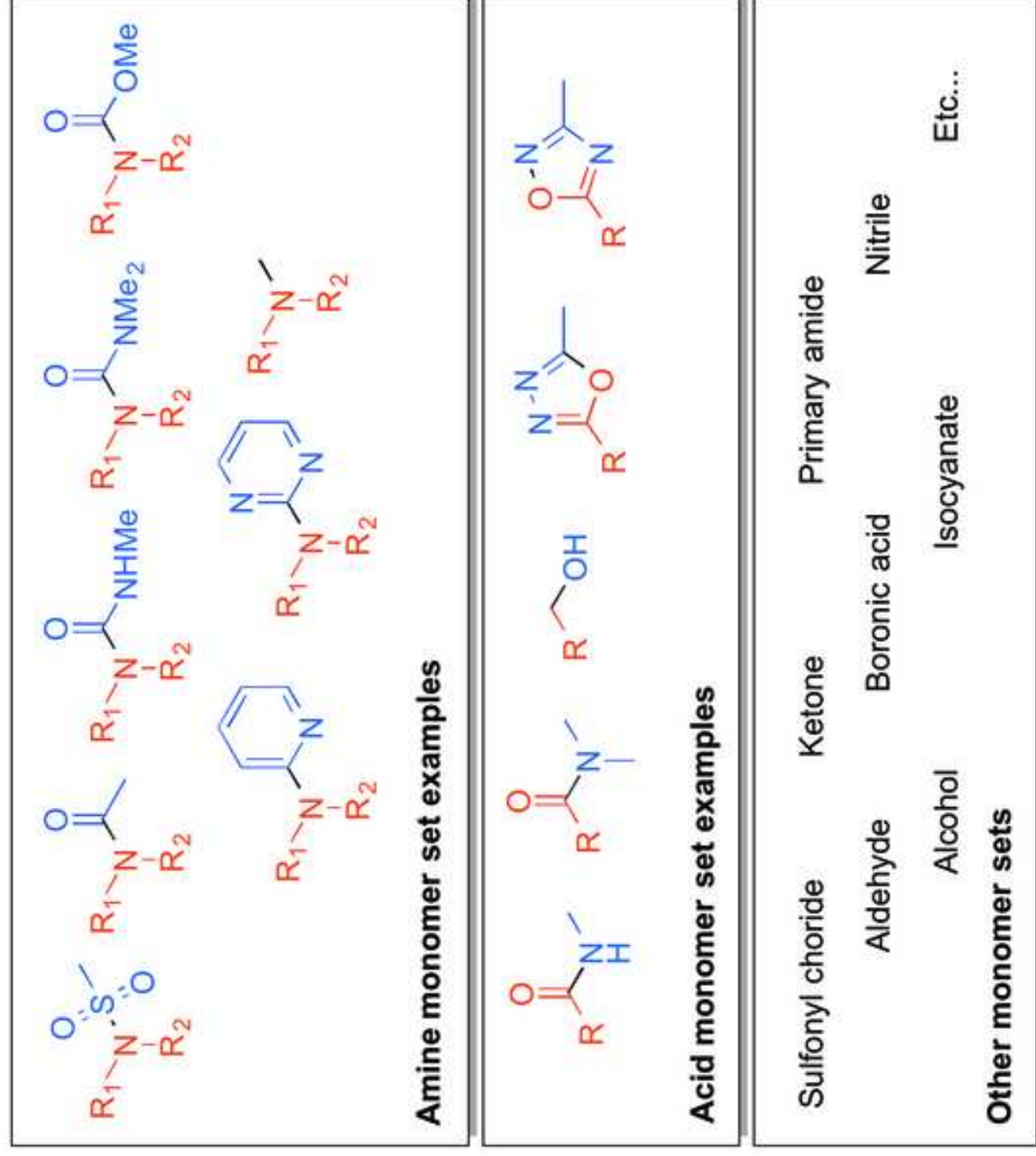


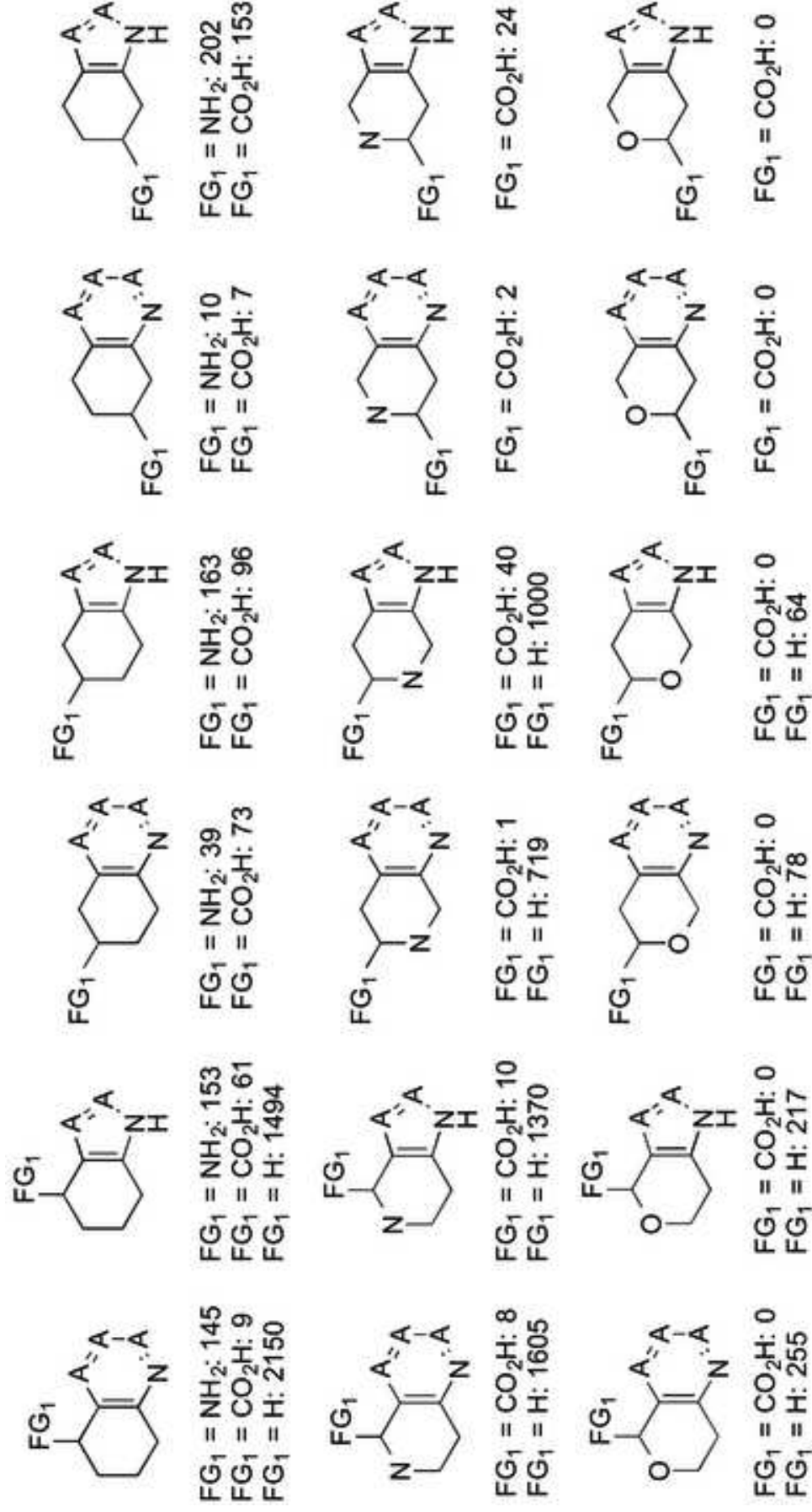
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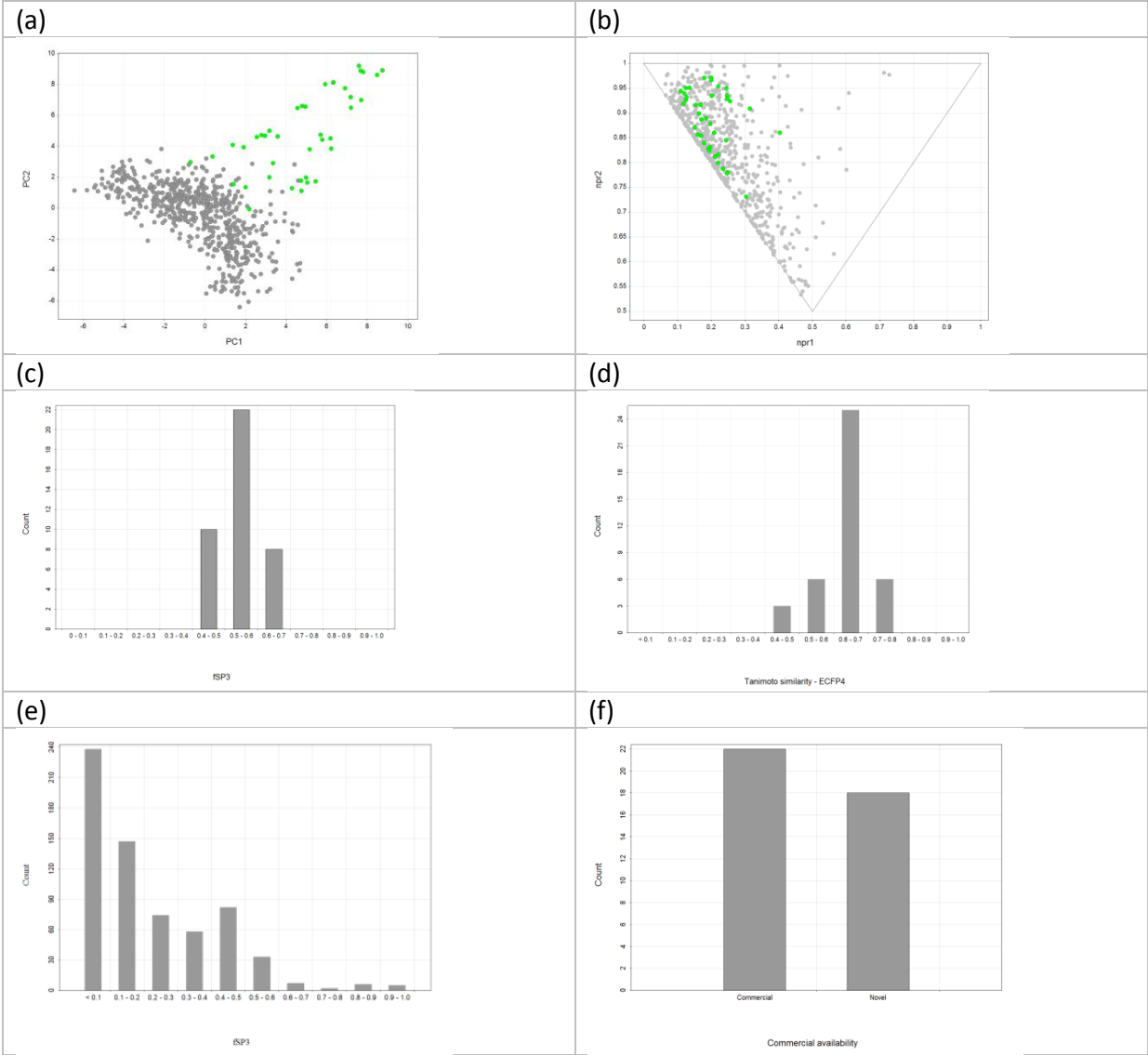
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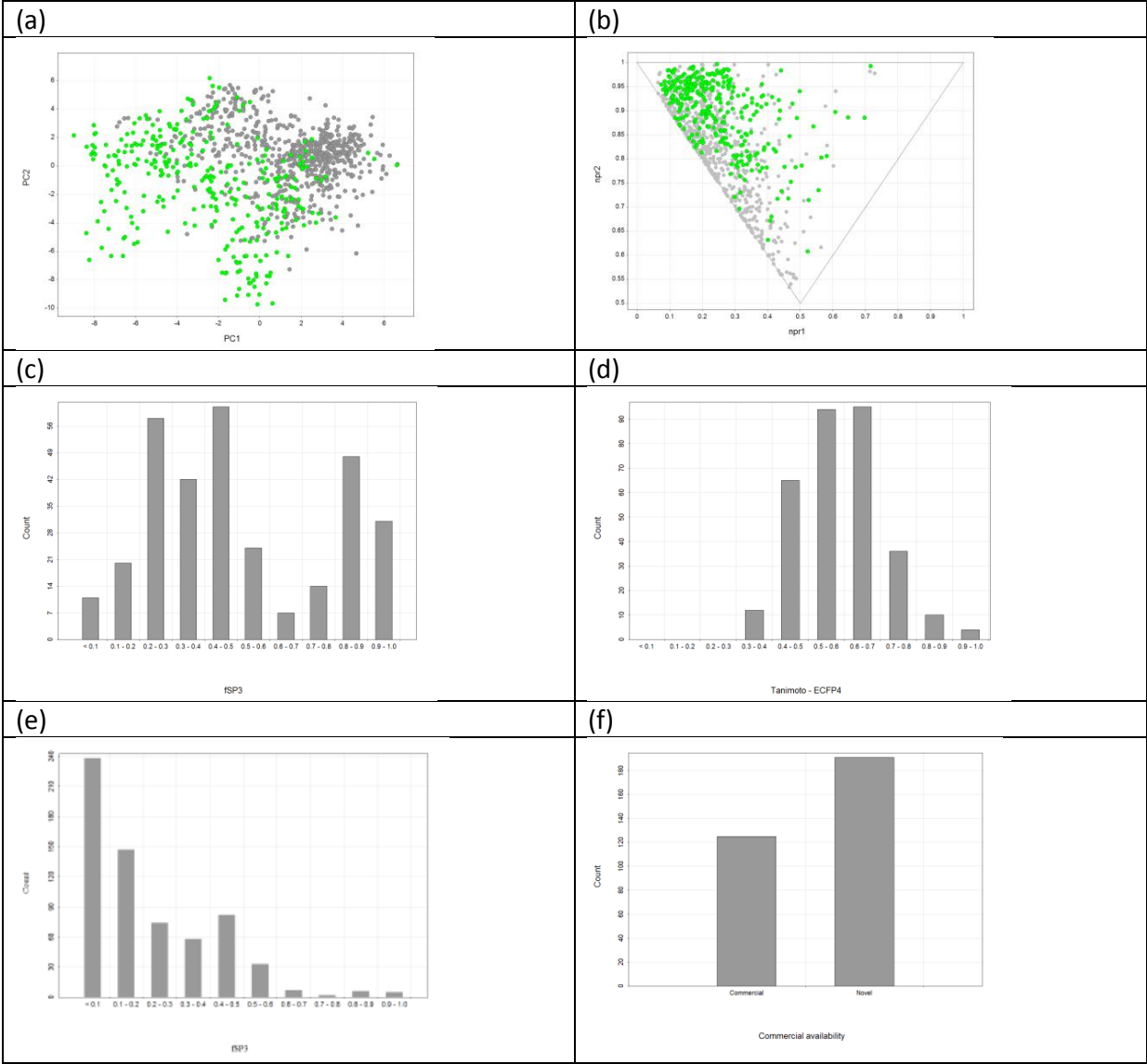




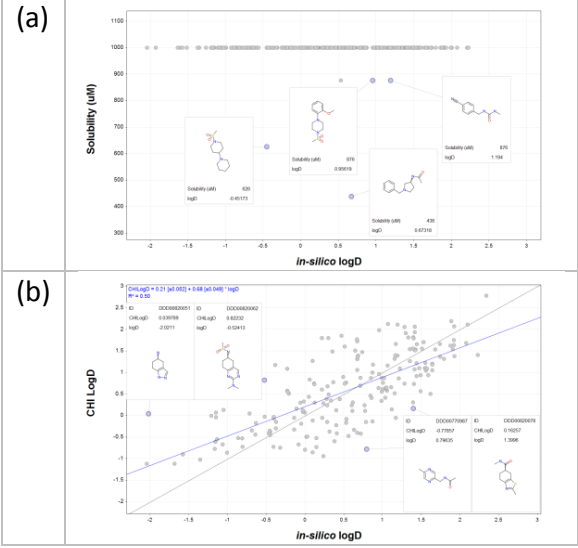
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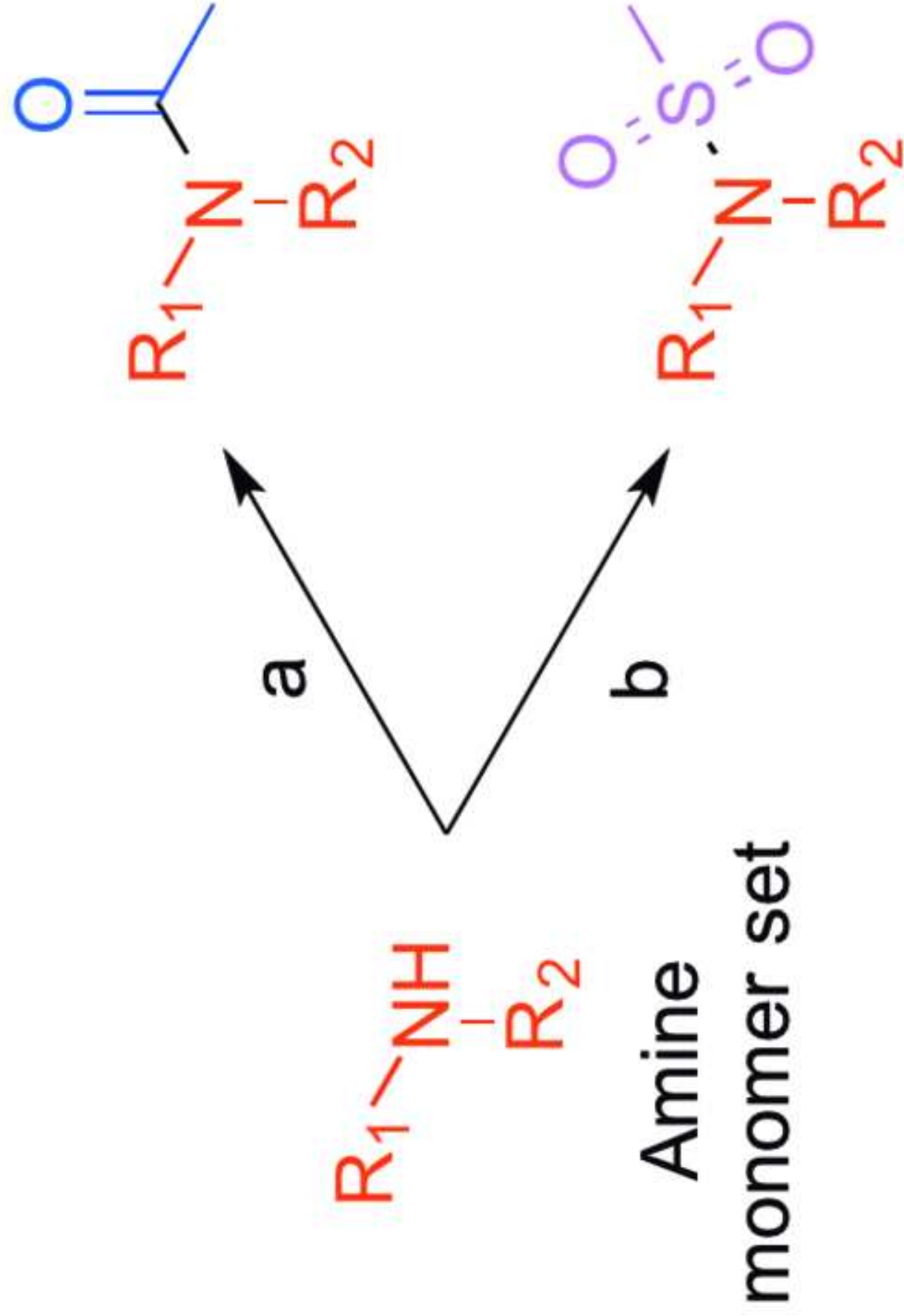


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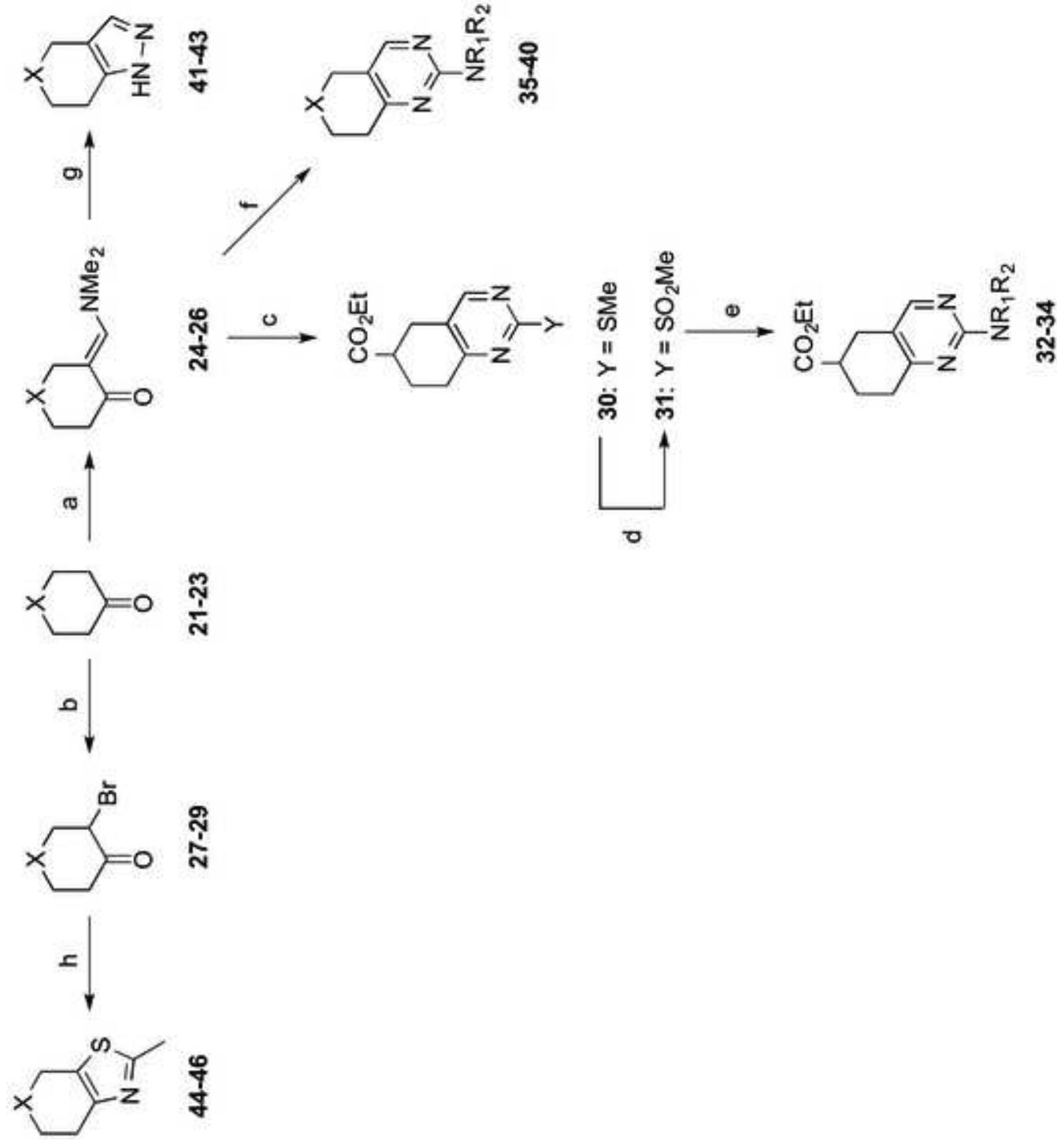
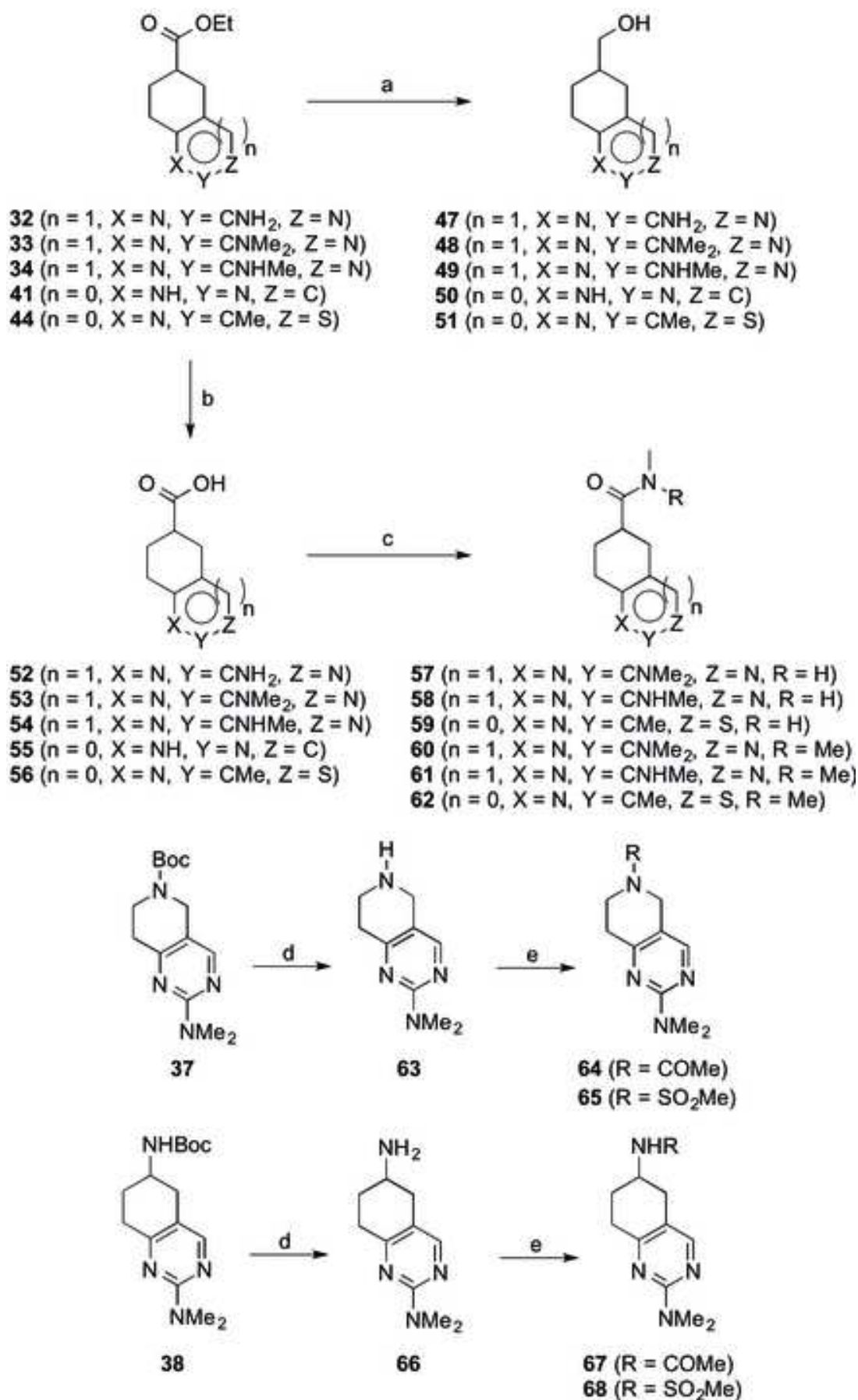


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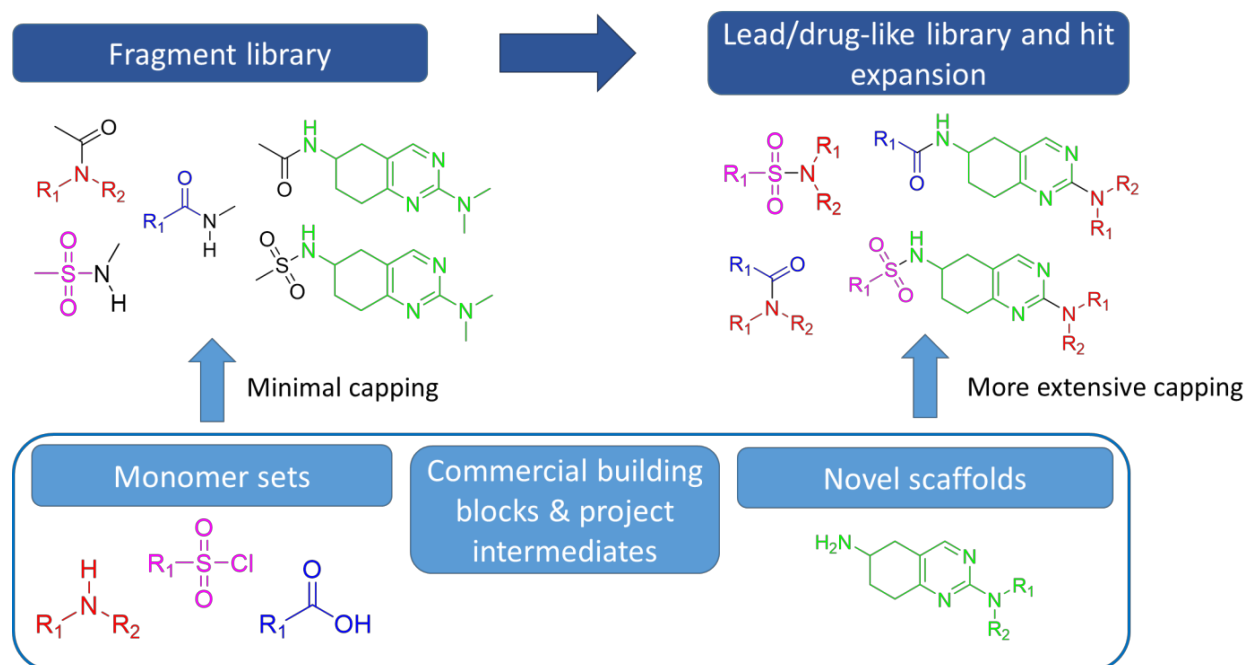
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Table 1. Descriptors and guide selection criteria employed for non-covalent reversible fragment libraries, monomer sets and lead-like libraries

Fragment library	Monomer sets	Lead-like library
HAC 5–18 LogP \leq 2.5 LogD \leq 2.5 HBD \leq 3 HBA \leq 6 PSA \leq 90 Å RotB \leq 3 Ar rings \leq 3	MW \leq 200 LogP \leq 2 HBD \leq 3 RotB \leq 3 Ar rings \leq 3	HAC 14–26 LogP –1 to 3 Ar rings \leq 3
Commercial availability, shape & diversity		
eMolecules sp ³ Content PMI (used for fragment library to impart understanding of shape where rotatable bonds \leq 3) PCA (ECFP4) ECFP4 fingerprint Medicinal chemists eye (Vortex)		
Structural alerts		
PAINS, Eli Lilly and DDU integrated set		

Physicochemical data were calculated using StarDrop™ (www.optibrium.com). clogD values were calculated at pH 7.4

Graphical Abstract



Highlights

- A platform for the production of novel, high quality fragment and lead-like libraries.
- Parameters for the design of monomer sets, fragments and lead-like libraries.
- Synthesis of multiple diverse scaffolds from common intermediates.
- Quality analysis of the fragments.